-- 17. (Amended) A method for first line treatment of type 2 diabetes, in a drug naïve human patient, which comprises administering to a drug naïve human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm, wherein the glyburide bioavailability is comparable to the glyburide bioavailability obtained with a separate administration of metformin and glyburide. --

REMARKS

Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 as amended are present.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Claims 37, 59, 60, 71, 72 and 73 have been amended to define the glyburide employed in the methods claimed as having a particle size distribution so that "where at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm."

Basis for these amendments are found in the Specification at page 15, lines 10 to 15 and in Claim 74.

Applicant's invention as claimed in Claim 37 is directed to a method for first line treatment of type 2 diabetes, in a drug naive human patient, which includes the step of administering to a drug naive human patient in need of treatment, as first line therapy, a low dose of a combination of metformin and glyburide, wherein the metformin in the low dose combination is administered in a daily dosage in an amount within the range from about 160 mg to about 750 mg, and the glyburide in said low dose combination is administered in a daily dosage in an amount within the range from about 0.5 to about 15 mg. The glyburide employed in the combination has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm.

Method Claims 59, 60, 71, 72 and 73 (as amended) now define the glyburide particle distribution as in amended Claim 37. In addition, Claims 75 to 78 define preferred glyburide particle size distributions.

Independent Claim 58 defines a method for treating diabetes employing a low dose of 250 mg metformin and 1.25 mg glyburide in first line treatment of diabetes.

Claims 37, 45-54, 58-60, 71-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Press Release 9/30/99: Bristol-Myers Squibb Files NDA for Novel Oral Antidiabetic Drug (PR) in view of Earle et al. for the reasons given in Paper No. 6.

In Paper No. 6, the Examiner maintains that:

> "PR discloses a method of using metformin and glyburide as initial therapy for patients with type 2 diabetes. The claims differ over PR in requiring a low dose combination. However, Earle et al. disclose that it is known in the art to use low-dose glyburide plus metformin. It would therefore be obvious to one of ordinary skill in the art to use the low dose glyburide of Earle et al. in the method of PR to yield the instant method, since PR discloses a method of using metformin and glyburide as initial therapy for patients with type 2 diabetes. One would be motivated by the desire to have a useful method to treat type 2 diabetes."

The Examiner also maintains that:

> "Applicant's argument that Erle et al. does not contemplate the instant doses of glyburide and metformin is not persuasive. The dose of glyburide is within the limits of claim 37 and in the absence of a showing of unexpected results in Declaration form no unobviousness is seen in the instant 750 mg of metformin over the 800 mg of metformin in Erle et al."

The cited press release (PR) discloses use of a fixed combination of metformin and glyburide as an initial therapy for patients with type 2 diabetes. There is no disclosure or suggestion of dosages of metformin or glyburide to be employed. Thus, the PR is totally devoid of Applicant's inventive concept as claimed, that is, use of a low dose combination of metformin and glyburide in initial or first line therapy for treating diabetes. In addition, there is no disclosure or suggestion in the PR of use of glyburide of certain particle size to enhance bioavailability when employed with metformin.

Accordingly, it is submitted that Applicant's invention as claimed is patentable over the PR.

The Erle et al. reference discloses a comparison of fixed combinations of "low-dose glyburide" plus metformin with high-dose glyburide alone in treating diabetes. Erle et al. discloses dosages of glyburide of 5, 7.5 or 10 mg/day and dosages of metformin of 800, 1200 or 1600 mg/day.

It is to be noted that the lowest dose of metformin employed by Erle et al. is 800 mg/day. Applicant requires a metformin dose of at most 750 mg/day. Furthermore, the Erle et al. study is not designed for initial or first line therapy. As indicated on page 62, column 1, "Patients who were on oral hypoglycaemic therapy stopped the treatment 2 weeks before inclusion." In addition, Erle et al. does not disclose or suggest employing specially sized glyburide as defined in Claims 37, 59, 60, 71, 72 ad 73 as well as Claims 75 to 78.

In view of the above, it is clear that Applicant's method as claimed as patentable over Erle et al.

It is submitted that Applicant's invention as claimed is patentable over a combination of PR taken with Erle et al.

Neither the PR reference nor Erle et al. discloses or suggests employing a combination of metformin and glyburide where the glyburide must have the special particle size distribution to achieve the required bioavailability properties. Furthermore, neither the PR reference nor Erle et al. discloses or suggests a method of treating diabetes employing a dosage of a maximum of 750 mg metformin per day. Thus, each of the references are devoid of Applicant's inventive concept so that the combination thereof is no more relevant than each reference taken alone.

Claim 58 defines a method employing a low dose of metformin of 250 mg and a low dose of glyburide of 1.25 mg in first line therapy of diabetes. None of the cited references taken alone or in combination discloses or suggests a method as defined in Claim 58.

Accordingly, it is submitted that Applicant's method as claimed in Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 is patentable over the combination of PR taken with Erle et al.

Claims 37, 45-54, 58-60, 71-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermann et al. alone or in view of 6,303,146.

The Examiner contends that:

> "Hermann et al (abstract, Table 1, among others) disclose a method for first line treatment of type 2 diabetes in a drug naive human patient comprising administering a low dose combination of metformin and glyburide. Dependent instant claims differ over Hermann et al in requiring specific particle sizes of glyburide and regimens and dosages. However, once a method of use is known it is within the skill of the artisan to determine the optimum dosages and regimens. Furthermore, 6.303,146 (claims, among others) discloses the instant particle sizes."

The Hermann et al. reference discloses a comparative study involving use of a combination of metformin and glibenclamide (also known as glyburide) for treating diabetes versus metformin alone and glibenclamide alone.

Hermann et al. disclose treating "patients with newly detected diabetes and patients earlier treated with diet alone "as well as" patients with previous antidiabetic mediation . . . after a wash-out period of 2-3 weeks." Patients were administered at dose level 1 "1 g metformin, 3.5 mg glibenclamide or 0.5 g metformin + 1.75 mg glibenclamide" (page 954, column 2). "Stepwise dose titration comprised at most six dose levels with dose escalation every 2 weeks . . ." (page 954, column 1). "Maximum dose was 3 g metformin + 14 mg glibenclamide in all groups." (page 954, column 2).

It is indicated on page 58, column 2, last paragraph that ". . . combination therapy did not reduce the typical side-effects of the drugs, at least not against glibenclamide monotherapy. The prevalence of all adverse and intercurrent medical events did not differ between treatment groups."

There is no disclosure or suggestion in Hermann et al. of employing glyburide of special particle size distribution as claimed herein in Claims 37, 59, 60, 71 to 73 and in Claims 75 to 78. This is essential in Applicant's method as claimed to achieve desired bioavailability. That the glyburide employed in combination with metformin in Hermann et al. may not have had adequate bioavailability may be seen from the fact that the prevalence of adverse and intercurrent medical events was no better when the combination was used as opposed to the individual components. Furthermore, some of the patients treated were previously medicated, and since there is no indication which patients received level 1 treatment, there is no actual disclosure of employing a low dose combination of metformin and glyburide in first line treatment of diabetes.

In view of the foregoing, it is submitted that Applicant's method as claimed is patentable over Hermann et al.

U.S. Patent No. 6,303,146 to Bonhomme has a U.S. filing date of July 14, 1999.

Applicant will submit a Declaration under Rule 131 which shows that Applicant's invention as claimed was conceived in the U.S. prior to July 14, 1999 and with due diligence reduced to practice thereafter, thereby removing U.S. Patent No. 6,303, 146 as a reference. The Declaration will be submitted within the next one-two months (or sooner). The inventor is no longer employed at the assignee company, namely, Bristol-Myers Squibb Company and so it will take some time to prepare the Declaration and have it executed.

The Examiner points out that a terminal disclaimer over application Serial No. 09/432,465 has not yet been filed. However, the claims of application Serial No. 9/432,465 will be amended so that they no longer encompass use of a combination of metformin and glyburide or other sulfonyl area. Accordingly, a terminal disclaimer will no longer be necessary.

With the filing of a Declaration under Rule 131, it is believed that Claims 37, 45 to 54, 58 to 60 and71 to 73 and 75 to 79 will be in condition for allowance.

Enclosed is a copy of WO 00/03742 as requested.

Respectfully submitted,

Burton Rodney

Burton Rodney
Attorney for Applicant
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Date: 11/14/02

MARKED-UP VERSION TO SHOW CHANGES

-- 37. (Twice Amended) A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide as greater than 60 μm, wherein the metformin in said low dose combination is administered in a daily dosage in an amount within the range from about 160 mg to about 750 mg, and the glyburide in said low dose combination is administered in a daily dosage in an amount within the range from about 0.5 to about 15 mg. --

-- 59. (Amended) A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm, wherein the starting daily dosage is 250 mg metformin and 1.25 mg glyburide twice a day or 500 mg metformin and 2.5 mg glyburide once a day--

-- 60. (Amended) A method for first line treatment of type 2 diabetes, in a drug naive human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm, wherein the starting daily dosage is 500 mg metformin and 5 mg glyburide. --

-- 71. (Amended) A method for lowering blood glucose in a hyperglycemic human patient, which comprises administering to a drug naive human patient in need of treatment, as first line therapy, a therapeutically effective amount of a low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm, wherein the metformin in said low dose combination is administered in a daily dosage in an amount within the range from about 160 mg to about 750 mg, and the glyburide in said low dose combination is administered in a daily dosage in an amount within the range from about 0.5 to about 15 mg. --

-- 72. (Amended) A method for decreasing insulin resistance, decreasing hemoglobinA_{1c}, increasing post-prandial insulin levels or decreasing post-prandial glucose excursion, individually or in any combination, in a human patient, which comprises administering to a drug naive human

patient in need of treatment as first line therapy, a therapeutically effective amount of a low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm, wherein the metformin in said low dose combination is administered in a daily dosage in an amount within the range from about 160 mg to about 750 mg, and the glyburide in said low dose combination is administered in a daily dosage in an amount within the range from about 0.5 to about 15 mg. --

-- 73. (Amended) A method for first line treatment of type 2 diabetes, in a drug naïve human patient, which comprises administering to a drug naïve human patient in need of treatment, as first line therapy, a therapeutically effective low dose of a combination of metformin and glyburide, where the glyburide has a particle size distribution so that at most 10% of the particles of the glyburide are less than 2 μm and at most 10% of the particles of the glyburide are greater than 60 μm, wherein the glyburide bioavailability is comparable to the glyburide bioavailability obtained with a separate administration of metformin and glyburide. --